

SEARCH REQUEST FORM

2-133

Examiner # (Mandatory): I. E. Crane Requester's Full Name: same

Art Unit 1623 Location (Bldg/Room#): 8D-14 Phone (circle 305 306 308) 4639

Serial Number: 09/288/344 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention See attached copy of claims

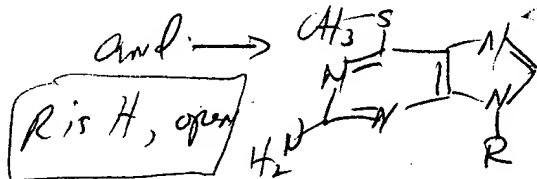
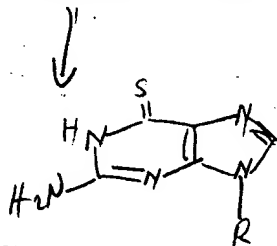
Inventors (please provide full names): "

Earliest Priority Date: 09/24/98

Keywords (include any known synonyms registry numbers, explanation of initialisms):

Please see claim 22 for key word disease conditions

Please search the keyword diseases with the following chemical formulas;. NOTE: Crohn's disease seems to be another term which might be helpful in this search.



Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

241
20
7
20
298

STAFF USE ONLY

Searcher: Mary

Searcher Phone #: _____

Searcher Location: _____

Date Picked Up: 7/19/99

Date Completed: _____

Clerical Prep Time: _____

Terminal Time: 13

Number of Databases: _____

Type of Search

____ N.A. Sequence

____ A.A. Sequence

____ Structure (#)

____ Bibliographic

____ Litigation1

____ Fulltext

____ Procurement

____ Other

Vendors (include cost where applicable)

____ STN

____ Questel/Orbit

____ Lexis/Nexis

____ WWW/Internet

____ In-house sequence systems (list)

____ Dialog

____ Dr. Link

____ Westlaw

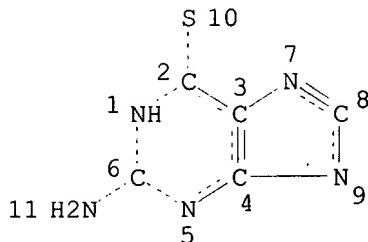
____ Other (specify)

Crane
288344

=> str

=> d 15 que stat;d 16 que stat;fil medl,hcaplus,biosis,embase;s 15 and 16

L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

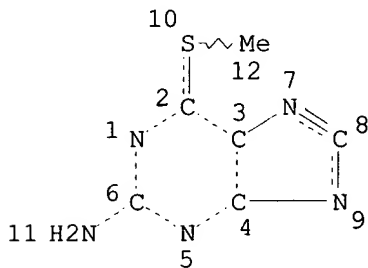
STEREO ATTRIBUTES: NONE
L5 214 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 514 ITERATIONS
SEARCH TIME: 00.00.01

*Mempro man
C-Haw Jani*

214 ANSWERS

L3 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L6 59 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 579 ITERATIONS
SEARCH TIME: 00.00.01

59 ANSWERS

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	241.20	540.42

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-18.36

FILE 'MEDLINE' ENTERED AT 16:42:01 ON 19 JUL 1999

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L7	0 FILE MEDLINE
L8	43 FILE HCAPLUS
L9	0 FILE BIOSIS
L10	0 FILE EMBASE

TOTAL FOR ALL FILES
 L11 43 L5 AND L6

=> s l11 and (gastrointestin? disorder or inflam? bowel disease or crohn)

L12	0 FILE MEDLINE
L13	0 FILE HCAPLUS
L14	0 FILE BIOSIS
L15	0 FILE EMBASE

TOTAL FOR ALL FILES
 L16 0 L11 AND (GASTROINTESTIN? DISORDER OR INFLAM? BOWEL DISEASE OR CROHN)

=> fil reg,e "6-mercaptopurine"/cn 5

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	20.51	560.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	0.00	-18.36

FILE 'REGISTRY' ENTERED AT 16:44:18 ON 19 JUL 1999
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STRUCTURE FILE UPDATES: 17 JUL 99 HIGHEST RN 228123-53-3
 DICTIONARY FILE UPDATES: 18 JUL 99 HIGHEST RN 228123-53-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
E1      1      6-MERCAPTOOCTANOIC ACID/CN
E2      1      6-MERCAPTOPURIN/CN
E3      1 --> 6-MERCAPTOPURINE/CN
E4      1      6-MERCAPTOPURINE 2'-DEOXYRIBONUCLEOSIDE/CN
E5      1      6-MERCAPTOPURINE 2'-DEOXYRIBOSIDE/CN
```

=> s e3;e "6-thioguanine"/cn 5

```
L17      1 6-MERCAPTOPURINE/CN
```

```
E1      1      6-THIOCYANATORIBOFLAVIN/CN
E2      1      6-THIOCYANOCARVACROL/CN
E3      1 --> 6-THIOGUANINE/CN
E4      1      6-THIOGUANINE PICRATE MONOHYDRATE/CN
E5      1      6-THIOGUANINE RIBONUCLEOSIDE/CN
```

=> s e3

```
L18      1 6-THIOGUANINE/CN
```

=> fil medl,hcaplus,biosis,embase,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.70	568.63
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-18.36

FILE 'MEDLINE' ENTERED AT 16:45:22 ON 19 JUL 1999

FILE 'HCAPLUS' ENTERED AT 16:45:22 ON 19 JUL 1999
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=> s (l17 or mercaptopurine) and (l18 or thioguanine)

```
L19      406 FILE MEDLINE
L20      478 FILE HCAPLUS
L21      453 FILE BIOSIS
L22      1549 FILE EMBASE
'CN' IS NOT A VALID FIELD CODE
L23      22 FILE WPIDS
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TOTAL FOR ALL FILES

L24 2908 (L17 OR MERCAPTOPURINE) AND (L18 OR THIOGUANINE)

=> s l24 and (gastrointestin? inflam? bowel disease or ibd or crohn?)

L25 5 FILE MEDLINE
L26 3 FILE HCAPLUS
L27 4 FILE BIOSIS
L28 5 FILE EMBASE
L29 1 FILE WPIDS

TOTAL FOR ALL FILES

L30 18 L24 AND (GASTROINTESTIN? INFLAM? BOWEL DISEASE OR IBD OR CROHN?)

=> dup rem l30

PROCESSING COMPLETED FOR L30

L31 10 DUP REM L30 (8 DUPLICATES REMOVED)

=> d tot all

L31 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 1999 ACS DUPLICATE 1

AN 1998:202674 HCAPLUS

DN 128:266250

TI Use of i.v. azathioprine or 6-mercaptopurine to treat Crohn's disease

IN Sandborn, William J.

PA Glaxo Wellcome Inc., USA

SO U.S., 11 pp.

CODEN: USXXAM

DT Patent

LA English

IC ICM A61K031-52

ICS A61K031-415

NCL 514262000

CC 1-7 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5733915	A	19980331	US 95-413783	19950330

AB A therapeutic method for the treatment of Crohn's disease is provided, comprising administering to a patient in need of said treatment an i.v. dose of azathioprine or 6-mercaptopurine, or a pharmaceutically acceptable deriv. thereof. Patients receiving high doses

of azathioprine administered via continuous i.v. infusion, showed a rapid increase in the levels of 6-thioguanine nucleotide in RBCs, concomitant with a rapid improvement in these patients clin. picture.

ST intravenous infusion azathioprine mercaptopurine Crohn disease

IT Corticosteroids, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (corticosteroid-intolerant Crohn's disease; i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT Diseases (animal)

(fistula, Crohn's fistulous disease; i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's

disease treatment)

IT Crohn's disease
Immunosuppressants
(i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT Infusions (drug delivery systems)
(i.v.; i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT Steroids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(steroid-dependent Crohn's disease; i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT 53-03-2, Prednisone
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study);

USES
(Uses)
(i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT 50-44-2, 6-Mercaptopurine
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT 446-86-6, Azathioprine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

IT 50-66-8, 6-Methylmercaptopurine 154-42-7D, 6-Thioguanine, nucleotides
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(i.v. infusion of azathioprine or 6-mercaptopurine for Crohn's disease treatment)

L31 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 1999 ACS DUPLICATE 2

AN 1998:189955 HCAPLUS

DN 128:252417

TI Azathioprine: state of the art in inflammatory bowel disease

AU Sandborn, W. J.

CS Mayo Clinic, Rochester, MN, USA

SO Scand. J. Gastroenterol., Suppl. (1998), 33(225), 92-99

CODEN: SJGSB8; ISSN: 0085-5928

PB Scandinavian University Press

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review with 37 refs. The use of 6-mercaptopurine (6MP) and its prodrug azathioprine (AZA) for inflammatory bowel disease (IBD) has increased in recent years. The pharmacol., patient response in controlled trials, new formulations and routes of administration and safety for these agents are reviewed. AZA is rapidly converted to 6MP, which is then further metabolized to the active metabolites, the 6-thioguanine nucleotides (6TGN). The half-life of 6TGN in erythrocytes is prolonged and weeks to months may be required to reach steady state. This prolonged time to 6TGN steady state may help explain the clin. observation that prolonged treatment (3-4 mo) with 6MP/AZA for

IBD is required before a therapeutic response occurs. Controlled trials of 6MP (1.5 mg/kg/d) or AZA (1.0-3.0 mg/kg/d) support the following

treatment indications for 6MP/AZA: inflammatory **Crohn's** disease; fistulizing **Crohn's** disease; steroid-sparing; and remission maintenance. Controlled trials of AZA (1.5-2.5 mg/kg/d) in UC have suggested efficacy for the indications of steroid sparing and remission maintenance, as well as a possible effect in chronically active disease. A therapeutic response appears to require .gtoreq. 17 wk for most patients, and it has been suggested that a greater cumulative dose of AZA may result in increased likelihood of response to AZA. A recent pilot study suggested that administration of an IV loading dose of AZA (20-44 mg/kg over 36 h) may decrease the time to response in **Crohn's** disease patients treated with AZA, perhaps by administering a portion of the necessary cumulative dose more rapidly. Two recent pharmacokinetic studies demonstrated that use of a delayed release oral AZA formulation which delivers AZA directly to the ileocolon markedly reduces systemic absorption of AZA. This "topical" or "local" approach to AZA treatment

of

IBD holds the promise of equal or improved efficacy with a significant redn. in toxicity, and dose-ranging clin. trials with delayed release oral AZA are planned in the near future. Side effects of AZA/6MP include pancreatitis, fever, nausea, leukopenia, infection, and

hepatitis.

It appears that the risk of malignancy during or following monotherapy with AZA/6MP for **IBD** is not increased relative to the general population. AZA/6MP therapy is efficacious and reasonably safe for selected patients with **IBD**. Indications for treatment with AZA/6MP include refractory **Crohn's** disease, fistulizing **Crohn's** disease, steroid-dependent **Crohn's** disease, **Crohn's** disease remission maintenance, and possibly refractory UC, steroid dependent UC, and UC remission maintenance. The use of these immune modifier drugs in patients with **IBD** represents a significant therapeutic advance.

ST azathioprine inflammation bowel disease therapy review

IT Inflammatory bowel diseases

(azathioprine in treatment of inflammatory bowel disease in humans)

IT 446-86-6, Azathioprine

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(azathioprine in treatment of inflammatory bowel disease in humans)

L31 ANSWER 3 OF 10 MEDLINE

AN 1998175511 MEDLINE

DN 98175511

TI Azathioprine: state of the art in inflammatory bowel disease.

AU Sandborn W J

CS Mayo Clinic, Rochester, MN, USA.

SO SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT, (1998) 225 92-9.

Ref: 37

Journal code: UCT. ISSN: 0085-5928.

CY Norway

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 199807

EW 19980703

AB INTRODUCTION: The use of 6-mercaptopurine (6MP) and its prodrug

azathioprine (AZA) for inflammatory bowel disease (IBD) has increased in recent years. The pharmacology, patient response in controlled trials, new formulations and routes of administration and safety for these agents are reviewed. PHARMACOLOGY: AZA is rapidly converted to 6MP, which is then further metabolized to the active metabolites, the 6-thioguanine nucleotides (6TGN). The half-life of 6TGN in erythrocytes is prolonged and weeks to months may be required to reach steady state. This prolonged time to 6TGN steady state may help explain the clinical observation that prolonged treatment (3-4 months) with 6MP/AZA for IBD is required before a therapeutic response occurs. CLINICAL RESPONSE: Controlled trials of 6MP (1.5 mg/kg/d) or AZA (1.0-3.0 mg/kg/d) support the following treatment indications for

6MP/AZA:

inflammatory Crohn's disease; fistulizing Crohn's disease; steroid-sparing; and remission maintenance. Controlled trials of AZA (1.5-2.5 mg/kg/d) in UC have suggested efficacy for the indications

of

steroid sparing and remission maintenance, as well as a possible effect

in

chronically active disease. A therapeutic response appears to require >

or

= 17 weeks for most patients, and it has been suggested that a greater cumulative dose of AZA may result in increased likelihood of response to AZA. A recent pilot study suggested that administration of an i.v.

loading

dose of AZA (20-44 mg/kg over 36 h) may decrease the time to response in Crohn's disease patients treated with AZA, perhaps by administering a portion of the necessary cumulative dose more rapidly.

Two

recent pharmacokinetic studies demonstrated that use of a delayed release oral AZA formulation which delivers AZA directly to the ileocolon

markedly

reduces systemic absorption of AZA. This 'topical' or 'local' approach to AZA treatment of IBD holds the promise of equal or improved efficacy with a significant reduction in toxicity, and dose-ranging clinical trials with delayed release oral AZA are planned in the near future. SAFETY: Side effects of AZA/6MP include pancreatitis, fever, nausea, leukopenia, infection, and hepatitis. It appears that the risk of malignancy during or following monotherapy with AZA/6MP for IBD is not increased relative to the general population. CONCLUSIONS: AZA/6MP therapy is efficacious and reasonably safe for selected patients with IBD. Indications for treatment with AZA/6MP include refractory Crohn's disease, fistulizing Crohn's disease, steroid-dependent Crohn's disease, Crohn's disease remission maintenance, and possibly refractory UC, steroid dependent UC, and UC remission maintenance. The use of these immune modifier drugs in patients with IBD represents a significant therapeutic advance.

CT

Check Tags: Human

Azathioprine: AD, administration & dosage

Azathioprine: AE, adverse effects

Azathioprine: PK, pharmacokinetics

*Azathioprine: TU, therapeutic use

Half-Life

Immunosuppressive Agents: AD, administration & dosage

Immunosuppressive Agents: AE, adverse effects

Immunosuppressive Agents: PK, pharmacokinetics

*Immunosuppressive Agents: TU, therapeutic use

Inflammatory Bowel Diseases: BL, blood

*Inflammatory Bowel Diseases: DT, drug therapy

Odds Ratio

Randomized Controlled Trials

6-Mercaptopurine: TU, therapeutic use
 RN 446-86-6 (Azathioprine); 50-44-2 (6-Mercaptopurine)
 CN 0 (Immunosuppressive Agents)

L31 ANSWER 4 OF 10 MEDLINE
 AN 97390640 MEDLINE
 DN 97390640
 TI 6-MP metabolite levels: a potential guide to Crohn's disease therapy.
 AU Sandborn W J
 SO GASTROENTEROLOGY, (1997 Aug) 113 (2) 690-2.
 Journal code: FH3. ISSN: 0016-5085.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
 EM 199710
 EW 19971005
 CT Check Tags: Human
 Antimetabolites: ME, metabolism
 Antimetabolites: TU, therapeutic use
 *Antimetabolites, Antineoplastic: ME, metabolism
 *Antimetabolites, Antineoplastic: TU, therapeutic use
 Azathioprine: TU, therapeutic use
 Chromatography, High Pressure Liquid
 Crohn Disease: BL, blood
 *Crohn Disease: DT, drug therapy
 Crohn Disease: ME, metabolism
 Methylthioinosine: BL, blood
 Methylthioinosine: ME, metabolism
 Thioguanine: BL, blood
 Thioguanine: ME, metabolism
 *6-Mercaptopurine: ME, metabolism
 *6-Mercaptopurine: TU, therapeutic use

RN 154-42-7 (Thioguanine); 342-69-8 (Methylthioinosine); 446-86-6 (Azathioprine); 50-44-2 (6-Mercaptopurine)
 CN 0 (Antimetabolites); 0 (Antimetabolites, Antineoplastic)

L31 ANSWER 5 OF 10 MEDLINE DUPLICATE 3
 AN 97038429 MEDLINE
 DN 97038429
 TI Quantitation of 6-thioguanine in peripheral blood leukocyte DNA in Crohn's disease patients on maintenance 6-mercaptopurine therapy.
 AU Cuffari C; Seidman E G; Latour S; Theoret Y
 CS Department of Pediatrics, Hopital Sainte-Justine, Universite de Montreal, QC, Canada.
 SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1996 May) 74 (5) 580-5.
 Journal code: CJM. ISSN: 0008-4212.
 CY Canada
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 199704
 EW 19970401
 AB The effects of 6-mercaptopurine (6MP) in inflammatory bowel disease are believed to be primarily mediated by its metabolite 6-thioguanine (6TG). Our aim was to develop an assay for measuring leukocyte DNA 6TG levels in patients with Crohn's disease, and to correlate them with levels of 6TG in erythrocytes. Heparinized blood was obtained from 15 adolescent Crohn's disease patients

receiving 6MP at an average dose of 1.3 mg.kg-1 day-1 (range 0.8-1.6 mg.kg-1 day-1) for a mean of 23.7 months (range 3-71 months). Leukocyte DNA and erythrocyte 6TG levels were measured by an HPLC assay. Leukocyte 6TG levels ranged from 100 to 2305 pmol/mg DNA, while erythrocyte 6TG levels ranged from 64 to 1038 pmol/8 x 10(8) red blood cells, demonstrating significant interpatient variability. Leukocyte DNA 6TG levels correlated directly with erythrocyte 6TG levels, as measured by

the

Spearman rank correlation coefficient ($p < 0.05$). The HPLC measurement of erythrocyte and leukocyte DNA 6TG levels can be useful clinically in monitoring compliance, as well as perhaps to tailor drug metabolite

levels

to achieve the desired clinical effect.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't

Adolescence

Adult

*Antimetabolites, Antineoplastic: BL, blood

Child

Chromatography, High Pressure Liquid: MT, methods

*Crohn Disease: BL, blood

Crohn Disease: DT, drug therapy

DNA: BL, blood

*DNA: CH, chemistry

Erythrocytes: CH, chemistry

*Immunosuppressive Agents: ME, metabolism

*Leukocytes: CH, chemistry

Leukocytes: ME, metabolism

Linear Models

Patient Compliance

*Thioguanine: BL, blood

*6-Mercaptopurine: ME, metabolism

RN 154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine);

9007-49-2 (DNA)

CN 0 (Antimetabolites, Antineoplastic); 0 (Immunosuppressive Agents)

L31 ANSWER 6 OF 10 MEDLINE

DUPLICATE 4

AN 97106897 MEDLINE

DN 97106897

TI 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity.

AU Cuffari C; Theoret Y; Latour S; Seidman G

CS Department of Pediatrics, Universite de Montreal, Canada.

SO GUT, (1996 Sep) 39 (3) 401-6.

Journal code: FVT. ISSN: 0017-5749.

CY ENGLAND: United Kingdom

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199703

EW 19970302

AB BACKGROUND: 6-Mercaptopurine (6-MP) has confirmed short and longterm efficacy in the treatment of IBD. However, the relation between its metabolism, efficacy, and side effects is not well understood.

AIMS: To assay 6-MP metabolites and to correlate levels with drug compliance, disease activity, and adverse effects of treatment. PATIENTS: Heparinised blood was obtained prior to daily administration of 6-MP in

25

adolescent Crohn's disease patients (14 ileocolitis, 11 colitis) receiving 1.2 (range 0.4-1.6) mg/kg/day for a mean of 17 (range 4-65)

months. METHODS: Erythrocyte free bases 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) were measured (pmol/8 x 10(8) red blood cells) using reverse phase high performance liquid chromatography. RESULTS: Disease activity (modified Harvey-Bradshaw index) improved significantly with 6-MP (p = 0.001). Clinical remission was achieved in 72% of patients, who stopped taking prednisone, or were successfully weaned to a low alternate day dose (< 0.4 mg/kg/OD). Remission correlated well with erythrocyte 6-TG (p < 0.05), but not 6-MMP levels. Neutropenia was associated with 6-MP use (p < 0.005), but did not correlate with erythrocyte 6-MP metabolite levels. One patient refractory to 6-MP had 6-TG, but no measureable 6-MMP production, suggesting deficient thiopurine methyl-transferase activity or poor compliance. 6-MP induced complications (hepatitis, pancreatitis, and marrow suppression) were generally associated with increased 6-MMP levels. CONCLUSIONS: These results suggest that high performance liquid chromatography measurement of erythrocyte 6-MP metabolites may provide a quantitative assessment of patient responsiveness and compliance to treatment. The data support an immunosuppressive role for 6-TG, and potential cytotoxicity of raised 6-MMP levels.

CT Check Tags: Human; Support, Non-U.S. Gov't
 Adolescence
 Adult
 Child
 Chromatography, High Pressure Liquid
 Crohn Disease: BL, blood
 *Crohn Disease: DT, drug therapy
 Erythrocytes: ME, metabolism
 *Immunosuppressive Agents: ME, metabolism
 *Immunosuppressive Agents: TU, therapeutic use
 Patient Compliance
 Thioguanine: BL, blood
 Treatment Outcome
 6-Mercaptopurine: AE, adverse effects
 *6-Mercaptopurine: ME, metabolism
 *6-Mercaptopurine: TU, therapeutic use

RN 154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine)
 CN 0 (Immunosuppressive Agents)

L31 ANSWER 7 OF 10 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1995:280768 BIOSIS
 DN PREV199598295068
 TI 6-Mercaptopurine (6-MP) metabolite measurement in IBD patients' neutrophils correlates with drug efficacy.
 AU Cuffari, C. (1); Seidman, E. (1); Theoret, Y.
 CS (1) Div. Gastroenterol., Dep. Pediatr., Cent. Recherche, Hop. Ste-Justine, Univ. Montreal, Montreal Canada

SO Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A803.
 Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week San Diego, California, USA May 14-17, 1995
 ISSN: 0016-5085.

DT Conference
 LA English
 CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
 Cytology and Cytochemistry - Human *02508
 Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508

Pathology, General and Miscellaneous - Therapy *12512
 Digestive System - Pathology *14006
 Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
 Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and
 Reticuloendothelial Pathologies *15006
 Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and
 Reticuloendothelial System *15008
 Pharmacology - Digestive System *22014
 Pharmacology - Immunological Processes and Allergy *22018
 Toxicology - Pharmacological Toxicology *22504
 Pediatrics *25000
 BC Hominidae *86215
 IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Cell Biology;
 Gastroenterology (Human Medicine, Medical Sciences); Hematology (Human
 Medicine, Medical Sciences); Pathology; Pediatrics (Human Medicine,
 Medical Sciences); Pharmacology; Toxicology
 IT Chemicals & Biochemicals
 6-MERCAPTOPURINE; 6-THIOGUANINE
 IT Miscellaneous Descriptors
 ADOLESCENT; ERYTHROCYTE; GASTROINTESTINAL AGENT; IMMUNOSUPPRESSANT-
 DRUG; INFLAMMATORY BOWEL DISEASE; LEUKOCYTE; LEUKOPENIA; MEETING
 ABSTRACT; 6-MERCAPTOPURINE; 6-THIOGUANINE
 ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 human (Hominidae)
 ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates
 RN 50-44-2 (6-MERCAPTOPURINE)
 154-42-7 (6-THIOGUANINE)

 L31 ANSWER 8 OF 10 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
 AN 92307418 EMBASE
 DN 1992307418
 TI The clinical pharmacology of 6-mercaptopurine.
 AU Lennard L.
 CS Univ. Dept. Medicine/Pharmacology, Section Pharmacology/Therapeutics,
 Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JP, United
 Kingdom
 SO European Journal of Clinical Pharmacology, (1992) 43/4 (329-339).
 ISSN: 0031-6970 CODEN: EJCPAS
 CY Germany
 DT Journal; General Review
 FS 016 Cancer
 022 Human Genetics
 025 Hematology
 026 Immunology, Serology and Transplantation
 037 Drug Literature Index
 038 Adverse Reactions Titles
 030 PharmacologyPharmacology
 LA English
 CT Medical Descriptors:
 *crohn disease: DT, drug therapy
 *graft rejection: DT, drug therapy
 *graft rejection: PC, prevention
 *kidney transplantation
 *leukemia: DT, drug therapy
 *metabolic activation
 clinical article
 controlled study

drug blood level
 drug efficacy
 drug metabolism
 enzyme activity
 erythrocyte
 female
 gastrointestinal disease: SI, side effect
 genetic polymorphism
 human
 intestine
 intravenous drug administration
 leukopenia: SI, side effect
 liver
 major clinical study
 male
 neutropenia: SI, side effect
 oral drug administration
 priority journal
 rash: SI, side effect
 review
 Drug Descriptors:
 *6 thioguanine nucleotide: CR, drug concentration
 *6 thioguanine nucleotide: AN, drug analysis
 *6 thioguanine nucleotide: PK, pharmacokinetics
 *azathioprine: DO, drug dose
 *azathioprine: AE, adverse drug reaction
 *azathioprine: PK, pharmacokinetics
 *azathioprine: CR, drug concentration
 *azathioprine: DT, drug therapy
 *drug metabolite: PK, pharmacokinetics
 *drug metabolite: AN, drug analysis
 *drug metabolite: CR, drug concentration
 *mercaptopurine: PK, pharmacokinetics
 *mercaptopurine: DO, drug dose
 *mercaptopurine: CB, drug combination
 *mercaptopurine: IT, drug interaction
 *mercaptopurine: CR, drug concentration
 *mercaptopurine: DT, drug therapy
 *mercaptopurine: AE, adverse drug reaction
 *tioguanine: DT, drug therapy
 *tioguanine: CR, drug concentration
 *tioguanine: PK, pharmacokinetics
 *tioguanine: AE, adverse drug reaction
 allopurinol: CB, drug combination
 allopurinol: IT, drug interaction
 hypoxanthine phosphoribosyltransferase: EC, endogenous compound
 methotrexate: IT, drug interaction
 methotrexate: DT, drug therapy
 methotrexate: CB, drug combination
 thiopurine methyltransferase: EC, endogenous compound
 xanthine oxidase: EC, endogenous compound
 unclassified drug
 (azathioprine) 446-86-6; (mercaptopurine) 31441-78-8,
 50-44-2, 6112-76-1; (tioguanine) 154-42-7; (allopurinol)
 315-30-0; (hypoxanthine phosphoribosyltransferase) 9016-12-0;
 (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (thiopurine
 methyltransferase) 67339-09-7; (xanthine oxidase) 9002-17-9

RN

L31

AN

DN

ANSWER 9 OF 10 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
 77155265 EMBASE
 1977155265

TI Clinical use of immunosuppressive drugs. II.
 AU Gerber N.L.; Steinberg A.D.
 CS Arthr. Rheum. Branch, Nat. Inst. Arthr. Metab. Dig. Dis., NIH, Bethesda,
 Md. 20014, United States
 SO Current Therapeutics, (1976) 17/6 (109-124).
 CODEN: CUTHDB
 DT Journal
 FS 037 Drug Literature Index
 026 Immunology, Serology and Transplantation
 030 Pharmacology
 LA English
 AB In controlled trials in patients with rheumatoid arthritis, high dose
 cyclophosphamide and azathioprine have been shown to be clearly
 beneficial
 when compared with placebo. In uncontrolled studies in dermatological
 diseases, azathioprine, 6 **mercaptopurine**, hydroxyurea,
 methotrexate, and azaribine have proven effective in treating psoriasis.
 Similarly, azathioprine, cyclophosphamide and methotrexate have all been
 used with success in treating pemphigus and pemphigoid, although none is
 effective in controlling acute pemphigus. In controlled studies in
 patients with psoriasis and psoriatic arthritis, azathioprine and
 methotrexate have been shown to be better than placebo. In hematological
 diseases, insufficient data has been accumulated to evaluate the efficacy
 of immunosuppressive drug treatment in patients with erythroid aplasia or
 sideroblastic anemia. Cyclophosphamide may be efficacious in inhibiting
 circulating anticoagulants in patients who need continued replacement of
 clotting factors. Azathioprine, 6 **mercaptopurine**,
 cyclophosphamide and vincristine have been used successfully in treating
 patients with idiopathic thrombocytopenic purpura, and some patients with
 auto immune hemolytic anemia may benefit from the addition of purine
 analogues. However, the use of immunosuppressive therapy seems to
 accelerate the presence of hematological malignancies in patients with
 macroglobulinemia. In gastro intestinal diseases, uncontrolled studies
 have shown nitrogen mustard, 6 **mercaptopurine** and azathioprine to
 be of modest benefit to patients with ulcerative colitis and **Crohn**
 's disease. In a controlled trial azathioprine plus prednisone proved
 more
 effective than prednisone alone in sustaining remission in patients with
Crohn's disease. In patient's with either chronic active hepatitis
 or primary biliary cirrhosis, however, there seems to be no benefit from
 immunosuppressive therapy for primary treatment of these diseases.
 CT Medical Descriptors:
 *blood disease
 *clinical study
 ***crohn disease**
 *drug comparison
 *immunosuppressive treatment
 *enteropathy
 *pemphigoid
 *pemphigus vulgaris
 *drug therapy
 *psoriasis
 *rheumatoid arthritis
 *thrombocytopenia
 *ulcerative colitis
 major clinical study
 therapy
 Drug Descriptors:
 *tioguanine
 *azaribine
 *azathioprine

*chlorambucil
 *chlormethine
 *cyclophosphamide
 *hydroxyurea
 *immunosuppressive agent
 *mercaptopurine
 *methotrexate
 *placebo
 *prednisone
 *vinblastine

RN (tioguanine) 154-42-7; (azaribine) 2169-64-4; (azathioprine) 446-86-6; (chlorambucil) 305-03-3; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (cyclophosphamide) 50-18-0; (hydroxyurea) 127-07-1; (**mercaptopurine**) 31441-78-8, **50-44-2**, 6112-76-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (prednisone) 53-03-2; (vinblastine) 865-21-4

L31 ANSWER 10 OF 10 MEDLINE
 AN 73202804 MEDLINE
 DN 73202804
 TI Cytotoxic drugs in treatment of nonmalignant diseases.
 AU Anonymous
 SO ANNALS OF INTERNAL MEDICINE, (1972 Apr) 76 (4) 619-42. Ref: 288
 Journal code: 5A6. ISSN: 0003-4819.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 197310
 CT Check Tags: Animal; Human
 Anti-Inflammatory Agents: PD, pharmacology
 Antineoplastic Agents: PD, pharmacology
 *Antineoplastic Agents: TU, therapeutic use
 Arthritis, Rheumatoid: DT, drug therapy
 Azathioprine: TU, therapeutic use
 Chlorambucil: TU, therapeutic use
 Colitis, Ulcerative: DT, drug therapy
Crohn Disease: DT, drug therapy
 Cyclophosphamide: TU, therapeutic use
 Hepatitis: DT, drug therapy
 Immune Complex Diseases: DT, drug therapy
 Immunosuppressive Agents: PD, pharmacology
 Infection: DT, drug therapy
 Liver Cirrhosis, Biliary: DT, drug therapy
 Lupus Erythematosus, Systemic: DT, drug therapy
 Methotrexate: TU, therapeutic use
 Nephrotic Syndrome: DT, drug therapy
 Ophthalmia, Sympathetic: DT, drug therapy
 Psoriasis: DT, drug therapy
Thioguanine
 Uveitis: DT, drug therapy
 Wegener's Granulomatosis: DT, drug therapy
6-Mercaptopurine: TU, therapeutic use

=> s (15 or 16 or 117 or 118 or mercaptopurine or thioguanine) and
 (gastrointest? or inflam? bowel? or ibd or crohn or colitis or lymphocytic)

L32 1327 FILE MEDLINE
 L33 118 FILE HCAPLUS
 L34 440 FILE BIOSIS

L35 2082 FILE EMBASE

COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID

The query entered contains both search terms created by structure-building or screen commands and text search terms. L#s created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

=> s (l5 or l6) and (gastrointest? or inflam? bowel? or ibd or crohn? or colitis)

L36 2 FILE MEDLINE

L37 2 FILE HCAPLUS

L38 0 FILE BIOSIS

L39 3 FILE EMBASE

COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID

The query entered contains both search terms created by structure-building or screen commands and text search terms. L#s created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

=> s seidman e?/au,in;s theoret y?/au,in

'IN' IS NOT A VALID FIELD CODE

L40 112 FILE MEDLINE

L41 25 FILE HCAPLUS

L42 181 FILE BIOSIS

'IN' IS NOT A VALID FIELD CODE

L43 87 FILE EMBASE

L44 1 FILE WPIDS

TOTAL FOR ALL FILES

L45 406 SEIDMAN E?/AU,IN

'IN' IS NOT A VALID FIELD CODE

L46 20 FILE MEDLINE

L47 15 FILE HCAPLUS

L48 35 FILE BIOSIS

'IN' IS NOT A VALID FIELD CODE

L49 21 FILE EMBASE

L50 0 FILE WPIDS

TOTAL FOR ALL FILES

L51 91 THEORET Y?/AU,IN

=> s l45 and l51

L52 1 FILE MEDLINE

L53 1 FILE HCAPLUS

L54 6 FILE BIOSIS

L55 2 FILE EMBASE

L56 0 FILE WPIDS

TOTAL FOR ALL FILES

L57 10 L45 AND L51

=> dup rem l57

PROCESSING COMPLETED FOR L57
L58 7 DUP REM L57 (3 DUPLICATES REMOVED)

=> d tot all;fil medl,hcaplus,biosis,embase

L58 ANSWER 1 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998253159 EMBASE
TI 6-Mercaptopurine metabolism in Crohn's disease [3] (multiple letters).
AU Ballinger A.; **Theoret Y.**; **Seidman E.G.**
CS A. Ballinger, Digestive Disease Research Centre, St Bartholomew's, Royal
London Sch. of Med./Dentistry, 2 Turner Street, Whitechapel, London E1
2AT, United Kingdom
SO Gut, (1998) 43/2 (301).
ISSN: 0017-5749 CODEN: GUTTAK
CY United Kingdom
DT Journal; Letter
FS 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
048 Gastroenterology
LA English
CT Medical Descriptors:
*crohn disease: DT, drug therapy
*crohn disease: ET, etiology
purine metabolism
drug metabolism
erythrocyte
disease activity
human
letter
priority journal
Drug Descriptors:
*mercaptopurine: DT, drug therapy
*mercaptopurine: PK, pharmacokinetics
*6 mercaptopurine derivative: PK, pharmacokinetics
RN (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1

L58 ANSWER 2 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:280731 BIOSIS
DN PREV199799579934
TI Intravenous 6-thioguanine (6-TG) prevents reactivation of trinitrobenzene
sulfonic acid (TNBS)-induced colitis.
AU Cuffari, Carmen; **Theoret, Yves**; Latour, Sylvain; **Seidman,**
Ernest G.
CS Dep. Pediatrics Pharmacol., Hopital Ste-Justine, Universite de Montreal,
Montreal Canada
SO Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A954.
~~Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the~~
American Gastroenterological Association Washington, D.C., USA May 11-14,
1997
ISSN: 0016-5085.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences,
Congresses, Review Annuals 00520
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Pharmacology - Digestive System *22014
Routes of Immunization, Infection and Therapy *22100

Laboratory Animals - General *28002
 BC Muridae *86375
 IT Major Concepts
 Digestive System (Ingestion and Assimilation); Methods and Techniques;
 Pathology; Pharmacology
 IT Chemicals & Biochemicals
 6-THIOGUANINE; TRINITROBENZENE SULFONIC ACID
 IT Miscellaneous Descriptors
 ANIMAL MODEL; DIGESTIVE SYSTEM; DIGESTIVE SYSTEM DISEASE; EFFECTS;
 GASTROINTESTINAL-DRUG; INTRAVENOUS ADMINISTRATION; PHARMACOLOGY;
 REACTIVATION PREVENTION; TRINITROBENZENE SULFONIC ACID-INDUCED
 COLITIS;
 6-THIOGUANINE
 ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 Sprague-Dawley rat (Muridae)
 ORGN Organism Superterms
 animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates;
 rodents; vertebrates
 RN 154-42-7 (6-THIOGUANINE)
 2508-19-2 (TRINITROBENZENE SULFONIC ACID)

L58 ANSWER 3 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1996:300477 BIOSIS
 DN PREV199699022833
 TI 6-Mercaptopurine (6-MP) metabolite levels in adult and pediatric IBD:
 Correlation with drug efficacy.
 AU Cuffari, C. (1); Theoret, Y.; Lahaie, R.; Seidman, E.
 CS (1) Div. Gastroenterol., Dep. Pediatrics, Univ. Montreal, Montreal, PQ
 Canada
 SO Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A890.
 Meeting Info.: 96th Annual Meeting of the American Gastroenterological
 Association and the Digestive Disease Week San Francisco, California, USA
 May 19-22, 1996
 ISSN: 0016-5085.
 DT Conference
 LA English
 CC General Biology - Symposia, Transactions and Proceedings of Conferences,
 Congresses, Review Annuals 00520
 Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
 Pathology, General and Miscellaneous - Inflammation and Inflammatory
 Disease *12508
 Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
 Digestive System - Pathology *14006
 Pharmacology - Clinical Pharmacology *22005
 Pharmacology - Digestive System *22014
 Pediatrics *25000
 BC Hominidae *86215
 IT Major Concepts
 Gastroenterology (Human Medicine, Medical Sciences); Metabolism;
 Pathology; Pediatrics (Human Medicine, Medical Sciences); Pharmacology
 IT Chemicals & Biochemicals
 6-MERCAPTOPURINE
 IT Miscellaneous Descriptors
 ANTIINFLAMMATORY-DRUG; CHILD; GASTROINTESTINAL-DRUG; INFLAMMATORY
 BOWEL
 DISEASE; MEETING ABSTRACT; 6-MERCAPTOPURINE
 ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name

human (Hominidae)
 ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates
 RN 50-44-2 (6-MERCAPTOPURINE)

L58 ANSWER 4 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1996:300478 BIOSIS
 DN PREV199699022834
 TI Pharmacokinetics explain the lack of short-term efficacy of
 6-mercaptopurine (6-MP) in the TNBS rat colitis model.
 AU Cuffari, C. (1); Theoret, Y.; Seidman, E.
 CS (1) Dep. Pediatric Gastroenterology, Hopital Ste-Justine, Univ. Montreal,
 Montreal, PQ Canada
 SO Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A890.
 Meeting Info.: 96th Annual Meeting of the American Gastroenterological
 Association and the Digestive Disease Week San Francisco, California, USA
 May 19-22, 1996
 ISSN: 0016-5085.
 DT Conference
 LA English
 CC Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
 Pathology, General and Miscellaneous - Inflammation and Inflammatory
 Disease *12508
 Pathology, General and Miscellaneous - Therapy *12512
 Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
 Digestive System - Pathology *14006
 Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
 Pharmacology - Digestive System *22014
 BC Muridae *86375
 IT Major Concepts
 Digestive System (Ingestion and Assimilation); Metabolism; Pathology;
 Pharmacology
 IT Chemicals & Biochemicals
 6-MERCAPTOPURINE; 6-THIOGUANINE
 IT Miscellaneous Descriptors
 ANTIINFLAMMATORY-DRUG; BIOAVAILABILITY; GASTROINTESTINAL-DRUG; MEETING
 ABSTRACT; 6-MERCAPTOPURINE; 6-THIOGUANINE
 ORGN Super Taxa
 Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 Muridae (Muridae)
 ORGN Organism Superterms
 animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals;
 rodents; vertebrates
 RN 50-44-2 (6-MERCAPTOPURINE)
 154-42-7 (6-THIOGUANINE)

L58 ANSWER 5 OF 7 MEDLINE DUPLICATE 1
 AN 97038429 MEDLINE
 DN 97038429
 TI Quantitation of 6-thioguanine in peripheral blood leukocyte DNA in
 Crohn's
 disease patients on maintenance 6-mercaptopurine therapy.
 AU Cuffari C; Seidman E G; Latour S; Theoret Y
 CS Department of Pediatrics, Hopital Sainte-Justine, Universite de Montreal,
 QC, Canada.
 SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1996 May) 74 (5) 580-5.
 Journal code: CJM. ISSN: 0008-4212.
 CY Canada
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English

FS Priority Journals
 EM 199704
 EW 19970401
 AB The effects of 6-mercaptopurine (6MP) in inflammatory bowel disease are believed to be primarily mediated by its metabolite 6-thioguanine (6TG). Our aim was to develop an assay for measuring leukocyte DNA 6TG levels in patients with Crohn's disease, and to correlate them with levels of 6TG in erythrocytes. Heparinized blood was obtained from 15 adolescent Crohn's disease patients receiving 6MP at an average dose of 1.3 mg.kg⁻¹ day⁻¹ (range 0.8-1.6 mg.kg⁻¹ day⁻¹) for a mean of 23.7 months (range 3-71 months). Leukocyte DNA and erythrocyte 6TG levels were measured by an HPLC assay. Leukocyte 6TG levels ranged from 100 to 2305 pmol/mg DNA, while erythrocyte 6TG levels ranged from 64 to 1038 pmol/8 x 10⁸ red blood cells, demonstrating significant interpatient variability. Leukocyte DNA 6TG levels correlated directly with erythrocyte 6TG levels, as measured by the Spearman rank correlation coefficient ($p < 0.05$). The HPLC measurement of erythrocyte and leukocyte DNA 6TG levels can be useful clinically in monitoring compliance, as well as perhaps to tailor drug metabolite levels to achieve the desired clinical effect.
 CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
 Adolescence
 Adult
 *Antimetabolites, Antineoplastic: BL, blood
 Child
 Chromatography, High Pressure Liquid: MT, methods
 *Crohn Disease: BL, blood
 Crohn Disease: DT, drug therapy
 DNA: BL, blood
 *DNA: CH, chemistry
 Erythrocytes: CH, chemistry
 *Immunosuppressive Agents: ME, metabolism
 *Leukocytes: CH, chemistry
 Leukocytes: ME, metabolism
 Linear Models
 Patient Compliance
 *Thioguanine: BL, blood
 *6-Mercaptopurine: ME, metabolism
 RN 154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine); 9007-49-2 (DNA)
 CN 0 (Antimetabolites, Antineoplastic); 0 (Immunosuppressive Agents)
 L58 ANSWER 6 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1995:280768 BIOSIS
 DN PREV199598295068
 TI 6-Mercaptopurine (6-MP) metabolite measurement in IBD patients' neutrophils correlates with drug efficacy.
 AU Cuffari, C. (1); Seidman, E. (1); Theoret, Y.
 CS (1) Div. Gastroenterol., Dep. Pediatr., Cent. Recherche, Hop. Ste-Justine,
 Univ. Montreal, Montreal Canada
 SO Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A803.
 Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week San Diego, California, USA May 14-17, 1995
 ISSN: 0016-5085.
 DT Conference
 LA English

CC General Biology - Symposia, Transactions and Proceedings of Conferences,
 Congresses, Review Annuals 00520
 Cytology and Cytochemistry - Human *02508
 Pathology, General and Miscellaneous - Inflammation and Inflammatory
 Disease *12508
 Pathology, General and Miscellaneous - Therapy *12512
 Digestive System - Pathology *14006
 Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
 Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and
 Reticuloendothelial Pathologies *15006
 Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and
 Reticuloendothelial System *15008
 Pharmacology - Digestive System *22014
 Pharmacology - Immunological Processes and Allergy *22018
 Toxicology - Pharmacological Toxicology *22504
 Pediatrics *25000
 BC Hominidae *86215
 IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Cell Biology;
 Gastroenterology (Human Medicine, Medical Sciences); Hematology (Human
 Medicine, Medical Sciences); Pathology; Pediatrics (Human Medicine,
 Medical Sciences); Pharmacology; Toxicology
 IT Chemicals & Biochemicals
 6-MERCAPTOPURINE; 6-THIOGUANINE
 IT Miscellaneous Descriptors
 ADOLESCENT; ERYTHROCYTE; GASTROINTESTINAL AGENT; IMMUNOSUPPRESSANT-
 DRUG; INFLAMMATORY BOWEL DISEASE; LEUKOCYTE; LEUKOPENIA; MEETING
 ABSTRACT; 6-MERCAPTOPURINE; 6-THIOGUANINE
 ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 human (Hominidae)
 ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates
 RN 50-44-2 (6-MERCAPTOPURINE)
 154-42-7 (6-THIOGUANINE)

 L58 ANSWER 7 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
 AN 1994:287640 BIOSIS
 DN PREV199497300640
 TI Measurement of erythrocyte 6-mercapto-purine (6MP) metabolites in IBD
 patients: Correlation with efficacy and toxicity.
 AU Cuffari, C.; Theoret, Y.; Duhaime, A.; Seidman, E.
 CS Div. Gastroenterol., Dep. Pediatrics, Hopital Ste-Justine, Univ.
 Montreal,
 Montreal Canada
 SO Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A1021.
 Meeting Info.: 95th Annual Meeting of the American Gastroenterological
 Association New Orleans, Louisiana, USA May 15-18, 1994
 ISSN: 0016-5085.
 DT Conference
 LA English
 CC General Biology - Symposia, Transactions and Proceedings of Conferences,
 Congresses, Review Annuals 00520
 Cytology and Cytochemistry - Human *02508
 Biochemical Studies - General 10060
 Pathology, General and Miscellaneous - Inflammation and Inflammatory
 Disease *12508
 Pathology, General and Miscellaneous - Therapy *12512
 Metabolism - General Metabolism; Metabolic Pathways *13002
 Digestive System - Pathology *14006

Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
 Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
 Pharmacology - Clinical Pharmacology *22005
 Pharmacology - Digestive System *22014
 Pharmacology - Immunological Processes and Allergy *22018
 Toxicology - Pharmacological Toxicology *22504
 BC Hominidae *86215
 IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Cell Biology;
 Gastroenterology (Human Medicine, Medical Sciences); Metabolism;
 Pathology; Pharmacology; Toxicology
 IT Chemicals & Biochemicals
 6-MERCAPTO-PURINE; AZATHIOPRINE
 IT Miscellaneous Descriptors
 ANTIINFLAMMATORY-DRUG; AZATHIOPRINE; INFLAMMATORY BOWEL DISEASE;
 MEETING ABSTRACT; PHARMACOKINETICS; 6-MERCAPTOPURINE
 ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 human (Hominidae)
 ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates
 RN 50-44-2 (6-MERCAPTO-PURINE)
 446-86-6 (AZATHIOPRINE)

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	ENTRY	SESSION
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=> s (l5 or l6) and (gastrointest? or inflam? bowel? or ibd or crohn? or colitis)

L59 2 FILE MEDLINE
 L60 2 FILE HCAPLUS
 L61 0 FILE BIOSIS
 L62 3 FILE EMBASE

TOTAL FOR ALL FILES

L63 7 (L5 OR L6) AND (GASTROINTEST? OR INFLAM? BOWEL? OR IBD OR CROHN?
 OR COLITIS)

=> dup rem l63

PROCESSING COMPLETED FOR L63
L64 7 DUP REM L63 (0 DUPLICATES REMOVED)

=> d tot all

L64 ANSWER 1 OF 7 MEDLINE

AN 96086788 MEDLINE

DN 96086788

TI An intravenous loading dose of azathioprine decreases the time to response

in patients with **Crohn's** disease.

AU Sandborn W J; Van O E C; Zins B J; Tremaine W J; Mays D C; Lipsky J J

CS Inflammatory Bowel Disease Clinic, Mayo Clinic, Rochester, Minnesota, USA.

NC FD-T-000-886 (FDA)

RR-00585 (NCRR)

SO ~~GASTROENTEROLOGY~~, (1995 Dec) 109 (6) 1808-17.

Journal code: FH3. ISSN: 0016-5085.

CY United States

DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199603

AB BACKGROUND & AIMS: Azathioprine, an effective therapy for **Crohn's** disease, is limited by a prolonged time to response. The aim of this study was to determine the safety and utility of a loading dose of azathioprine to decrease the time to response in patients with **Crohn's** disease. METHODS: Twelve patients were studied: 6 with 13 fistulae and 6 with inflammatory disease. All patients received an intravenous infusion of azathioprine (50 mg/h for 36 hours). Response was determined by physical and radiographic examination for fistulae and by the **Crohn's** Disease Activity Index for inflammatory disease. Erythrocyte concentrations of azathioprine metabolites were measured by chromatography. RESULTS: Seven of 13 fistulae closed by week 4, and three had a temporary decrease in drainage. One fistula improved at week 16.

Two

fistulae failed to improve. Four of 6 patients with inflammatory disease achieved remission, and 1 improved temporarily. Improvement was rapid (< or = 4 weeks). Peak concentrations of azathioprine metabolites occurred within 3 days. Clinical response did not correlate with azathioprine metabolite concentrations at the azathioprine dose studied. No adverse events occurred. CONCLUSIONS: An 1800-mg intravenous loading dose of azathioprine is safe and may decrease the time to response to < or = 4 weeks in patients with **Crohn's** disease. Correlation between clinical response and azathioprine metabolite concentrations at larger azathioprine doses should be determined.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Adult

Aged

*Azathioprine: AD, administration & dosage

Azathioprine: ME, metabolism

Azathioprine: TU, therapeutic use

Crohn Disease: BL, blood

***Crohn Disease**: DT, drug therapy

Erythrocytes: ME, metabolism

Guanine Nucleotides: BL, blood

*Immunosuppressive Agents: AD, administration & dosage

Immunosuppressive Agents: ME, metabolism
 Immunosuppressive Agents: TU, therapeutic use
 Infusions, Intravenous
 Methyltransferases: BL, blood
 Middle Age
 Remission Induction
 Thionucleotides: BL, blood
 Time Factors

RN 15867-02-4 (6-thioguanilyc acid); 446-86-6 (Azathioprine)
 CN EC 2.1.1. (Methyltransferases); EC 2.1.1.67 (thiopurine
 methyltransferase); 0 (Guanine Nucleotides); 0 (Immunosuppressive
 Agents);
 0 (Thionucleotides)

L64 ANSWER 2 OF 7 MEDLINE
 AN 85254536 MEDLINE
 DN 85254536
 TI Phase II trials of hexamethylmelamine, dianhydrogalactitol, razoxane, and
 beta-2'-deoxythioguanosine as single agents against advanced measurable
 tumors of the pancreas. **Gastrointestinal** Tumor Study Group.
 AU Anonymous
 NC N01-CM-57032-57035 (NCI)
 N01-CM-53844 (NCI)
 N01-CM-67093-67097 (NCI)
 SO CANCER TREATMENT REPORTS, (1985 Jun) 69 (6) 713-6.
 Journal code: CNM. ISSN: 0361-5960.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals; Cancer Journals
 EM 198511
 AB Phase II trials of several single agents demonstrated only minimal
 objective response rates in patients with pancreatic carcinoma and
 measurable tumors: hexamethylmelamine (7%; four responses among 55
 patients); dianhydrogalactitol (2.5%; one response among 40 patients);
 razoxane (7%; two responses among 29 patients); and beta-2'-
 deoxythioguanosine (6%; two responses among 32 patients). Among patients
 with a good performance status (0-2) and no prior chemotherapy, response
 rates were 8% for hexamethylmelamine (two responses among 26 patients);
 8%
 for dianhydrogalactitol (one response among 13 patients); 8% for razoxane
 (one response among 12 patients); and 10% for beta-2'-deoxythioguanosine
 (two responses among 20 patients). None of these agents given by the
 methods of this study offers substantive benefit to the patient with
 advanced pancreatic cancer.
 CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
 *Adenocarcinoma: DT, drug therapy
 *Altretamine: TU, therapeutic use
 Antineoplastic Agents: TO, toxicity
 *Antineoplastic Agents: TU, therapeutic use
 *Deoxyguanosine: AA, analogs & derivatives
 Deoxyguanosine: TU, therapeutic use
 *Dianhydrogalactitol: TU, therapeutic use
 Drug Evaluation
 Leukopenia: CI, chemically induced
 *Pancreatic Neoplasms: DT, drug therapy
 *Piperazines: TU, therapeutic use
 *Razoxane: TU, therapeutic use
 *Sugar Alcohols: TU, therapeutic use
 *Thionucleosides: TU, therapeutic use
 Thrombocytopenia: CI, chemically induced

*Triazines: TU, therapeutic use
RN 21416-87-5 (Razoxane); 23261-20-3 (Dianhydrogalactitol); 645-05-6
(Altretamine); 789-61-7 (beta-2'-deoxythioguanosine); 961-07-9
(Deoxyguanosine)
CN 0 (Antineoplastic Agents); 0 (Piperazines); 0 (Sugar Alcohols); 0
(Thionucleosides); 0 (Triazines)

L64 ANSWER 3 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 85181695 EMBASE

DN 1985181695

TI Phase II trials of hexamethylmelamine, dianhydrogalactitol, razoxane, and
.beta.-2'-deoxythioguanosine as single agents against advanced measurable
tumors of the pancreas.

SO Cancer Treatment Reports, (1985) 69/6 (713-716).

CODEN: CTRRDO

CY United States

DT Journal

FS 038 Adverse Reactions Titles

037 Drug Literature Index

016 Cancer

048 Gastroenterology

006 Internal Medicine

LA English

AB Phase II trials of several single agents demonstrated only minimal
objective response rates in patients with pancreatic carcinoma and
measurable tumors: hexamethylmelamine (7%; four responses among 55
patients); dianhydrogalactitol (2.5%; one response among 40 patients);
razoxane (7%; two responses among 29 patients); and .beta.-2'-
deoxythioguanosine (6%; two responses among 32 patients). Among patients
with a good performance status (0-2) and no prior chemotherapy, response
rates were 8% for hexamethylmelamine (two responses among 26 patients);

8% for dianhydrogalactitol (one response among 13 patients); 8% for razoxane
(one response among 12 patients); and 10% for

.beta.-2'-deoxythioguanosine
(two responses among 20 patients). None of these agents given by the
methods of this study offers substantive benefit to the patient with
advanced pancreatic cancer.

CT Medical Descriptors:

*adverse drug reaction

*bone marrow depression

*cancer chemotherapy

*delusion

*drug comparison

*drug efficacy

*eye toxicity

*gastrointestinal toxicity

*neurotoxicity

*pancreas carcinoma

*drug therapy

*phase 2 clinical trial

*vertigo

*visual impairment

*vomiting

pancreas

priority journal

blood and hemopoietic system

visual system

therapy

intoxication

nervous system

intravenous drug administration
 human
 clinical article
 Drug Descriptors:
 *altretamine
 *deoxythioguanosine
 *dianhydrogalactitol
 *razoxane
 RN (altretamine) 15468-34-5, 2975-00-0, 645-05-6; (deoxythioguanosine)
 2133-81-5, 789-61-7; (dianhydrogalactitol) 23261-20-3;
 (razoxane) 21416-67-1, 21416-87-5, 24584-09-6, 24613-06-7

 L64 ANSWER 4 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
 AN 85181690 EMBASE
 DN 1985181690
 TI Phase I evaluation of .beta.-2'-deoxythioguanosine in pediatric patients
 with leukemia.
 AU Higgins G.R.; Jamin D.C.; Shore N.A.; et al.
 CS Division of Hematology-Oncology, Childrens Hospital of Los Angeles, Los
 Angeles, CA 90054, United States
 SO Cancer Treatment Reports, (1985) 69/6 (699-701).
 CODEN: CTRRDO
 CY United States
 DT Journal
 FS 038 Adverse Reactions Titles
 037 Drug Literature Index
 016 Cancer
 025 Hematology
 007 Pediatrics and Pediatric Surgery
 030 Pharmacology

 LA English
 AB Thirty-one pediatric patients with acute leukemia who had relapsed on
 either 6-mercaptopurine or 6-thioguanine were treated with
 .beta.-2'-deoxythioguanosine, which was administered as an iv infusion
 every 12 hours for three or six doses every 2 weeks. Severe nausea and
 vomiting and urate nephropathy were the dose-limiting toxic effects.
 Therapeutic responses occurred in four of 24 children with acute
 lymphocytic leukemia and in two of seven with acute nonlymphoblastic
 leukemia.
 CT Medical Descriptors:
 *acute lymphocytic leukemia
 *acute nonlymphocytic leukemia
 *adverse drug reaction
 *cancer combination chemotherapy
 *cancer recurrence
 *childhood cancer
 *drug efficacy
 *gastrointestinal toxicity
 *leukemia
 *nausea
 *nephrotoxicity
 *drug therapy
 *rash
 *skin toxicity
 *uric acid nephropathy
 *vomiting
 acute granulocytic leukemia
 acute lymphoblastic leukemia
 kidney disease
 toxicity
 kidney

intoxication
 priority journal
 therapy
 blood and hemopoietic system
 intravenous drug administration
 human
 child
 clinical article
 Drug Descriptors:
 *deoxythioguanosine
 *mercaptopurine
 *tioguanine
 allopurinol
 RN (deoxythioguanosine) 2133-81-5, 789-61-7;
 (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (tioguanine) 154-42-7;
 (allopurinol) 315-30-0
 CO National cancer institute (United States)

L64 ANSWER 5 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
 AN 83171004 EMBASE
 DN 1983171004
 TI Combination chemotherapy containing semustine (MeCCNU) in patients with
 advanced colorectal cancer previously treated with 5-fluorouracil (5-Fu).
 AU Engstrom P.F.; MacIntyre J.M.; Muggia F.; et al.
 CS Amer. Oncol. Hosp., Philadelphia, PA, United States
 SO American Journal of Clinical Oncology: Cancer Clinical Trials, (1983) 6/2
(175-180).
 CODEN: AJCODI
 CY United States
 DT Journal
 FS 038 Adverse Reactions Titles
 037 Drug Literature Index
 016 Cancer
 020 Gerontology and Geriatrics
 LA English
 AB Two hundred thirty-two patients with advanced measurable colorectal
 cancer
 previously treated with 5-fluorouracil (5-Fu) were randomized to one of
 the following treatments: A) semustine (MeCCNU) plus vincristine (VCR);
 B)
 MeCCNU plus dacarbazine (DTIC); C) MeCCNU plus DTIC plus VCR; D) MeCCNU
 plus beta-2'-deoxythioguanosine (.beta.-TGdR). Platelet nadirs
 <50,000/mm3
 were noted in 9% (Treatment A) to 19% (D) of the patients while WBC
 nadirs
 <2,000/mm3 were noted in 7% (B) to 12% (C,D) of the patients. Severe
 vomiting was noted in 2% (D) to 14% (B) of the patients. The partial
 response rates and median survival times from date of randomization were
 as follows: Treatment A: 3/54 (6%), 19 weeks; B: 9/59 (16%), 28 weeks; C:
 3/60 (5%), 25 weeks; D: 2/59 (4%), 19 weeks. Differences in response rate
 and median survival are not statistically significant.
 CT Medical Descriptors:
 *adverse drug reaction
 *bone marrow depression
 *cancer combination chemotherapy
 *colon carcinoma
 *drug comparison
 *gastrointestinal toxicity
 *neurotoxicity
 *drug therapy
 *rectum carcinoma

*vomiting
cancer chemotherapy
intoxication
nervous system
blood and hemopoietic system
therapy
intravenous drug administration
human
large intestine
major clinical study
Drug Descriptors:
*dacarbazine
*deoxythioguanosine
*fluorouracil
*semustine
*vincristine

RN (dacarbazine) 4342-03-4; (deoxythioguanosine) 2133-81-5,
789-61-7; (fluorouracil) 51-21-8; (semustine) 13909-09-6;
(vincristine) 57-22-7

L64 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 1999 ACS

AN 1973:413635 HCAPLUS

DN 79:13635

TI Preclinical toxicologic studies of .beta.-thioguanine deoxyriboside
(NSC-71261)

AU Henry, M. C.; Morrison, R. K.; Brown, D. E.; Marlow, M.; Davis, R.;
Cooney, D. A.

CS Res. Inst., Illinois Inst. Technol., Chicago, Ill., USA

SO Cancer Chemother. Rep., Part 3 (1973), 4(1), 41-9

CODEN: CCYPBY

DT Journal

LA English

CC 1-5 (Pharmacodynamics)

AB In dogs, .beta.-thioguanine deoxyriboside (I) [789-61-7]
toxicity was characterized by the early development of pyrexia,
leukopenia, anorexia, tonsillitis, pharyngitis, and marked
thrombocytopenia; anemia developed later. In rhesus monkeys, anemia and
leukopenia developed early while moderate reductions in the thrombocyte
count occurred later. The leukopenia is essentially a granulocytopenia

in both species. Hepatic and **gastrointestinal** toxic effects of I
were evident in a few animals treated at high dose levels. The toxicity
of I in mice and dogs was enhanced when I was administered in split doses
rather than as a single injection.

ST Thioguanine deoxyriboside toxicity

IT 1688-22-8

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of)

L64 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 1999 ACS

AN 1973:413459 HCAPLUS

DN 79:13459

TI Chronic toxicity of various classes of cancer chemotherapeutic agents

AU Henry, Mary C.

CS Res. Inst., Illinois Inst. Technol., Chicago, Ill., USA

SO U. S. Nat. Tech. Inform. Serv., PB Rep. (1972), No. 214546/4, 336 pp.
Avail.: NTIS

From: Govt. Rep. Announce. (U.S.) 1973, 73(7), 79

CODEN: XPBRCA

DT Report

LA English

CC 1-5 (Pharmacodynamics)

AB .alpha.-2'-Deoxythioguanosine (I) [2133-81-5] toxicity in dogs
and monkeys is characterized by the early development of emesis,
diarrhea,

anorexia, and leukopenia, with later development of thrombocytopenia and
neutropenia. The drug has low toxicity, and produced mortality in dogs
only after daily administration of 4000 mg/m² for 4 days.

Gastrointestinal toxicity and significant thrombocytopenia were
present only at high dose levels. A lethal dose was not found for
monkeys

on this dose regimen.

ST deoxythioguanosine toxicity leukopenia; thrombocytopenia neutropenia
deoxythioguanosine toxicity

IT 2133-81-5

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of)

=> disc bio